depends on whether those skilled in the art would understand the scope of the claim when the claim is read in the light of the specification." *North American Vaccine Inc. v. American Cyanamid Co.*, 28 U.S.P.Q.2d 1333, 1339 (Fed. Cir. 1993). Applicants respectfully submit that one of ordinary skill in the art, reading the specification, would readily understand what is meant by the term "substituted." The specification clearly provides a definition for the term "substituted." For example, the term "substituted alkyl" and "substituted aryl" are both defined (*See, e.g.*, Specification, page 4, lines 14-30 and page 5, lines 9-18, respectively). Accordingly, one of ordinary skill in the art, reading the disclosure, would readily understand what scope is meant by the term "substituted."

Furthermore, a large number of decisions have held that terms like "substituted alkyl" and "substituted aryl" are not indefinite under 35 U.S.C. § 112, second paragraph. For example, in *Ex parte Lewis et al.*, 197 U.S.P.Q. 543 (Bd. Pat. App. & Inter. 1977), the claim term "substituted alkyl" was found definite *(See also, Ex parte Breuer*, 1 U.S.P.Q.2d 1906 (Bd. Pat. App. & Inter. 1986) (the claim terms "substituted aryl", "substituted alkyl", and "heterocycles" are definite); *Cf. Ex parte Takeyama et al.*, 2000 WL 33149253 (Bd. Pat. App. & Inter. 2000). In *Ex parte Lewis et al.* claim 1 as issued in the corresponding patent, 4,105,431, reads as follows:

> A composition for inhibiting the growth of bacteria, fungi, or algae comprising an agronomically-acceptable carrier and, in an amount which is effective to adversely affect the growth of bacteria, fungi, or algae, a compound of the formula . . . wherein Y is an unsubstituted or substituted alkyl, alkenyl, or alkynyl group of 1 to 18 carbon atoms, an unsubstituted or substituted cycloalkyl group having a 3 to 6 carbon atom ring and up to 12 carbon atoms, an unsubstituted or substituted aralkyl group of up to 10 carbon atoms, or an unsubstituted or substituted aryl group of up to 10 carbon atoms.

The Examiner rejected what eventually became issued claim 1 under 35 U.S.C. § 112, second paragraph, stating that the term "substituted" rendered the claim too broad and indefinite. The Board reversed stating that the specification adequately teaches how to make and use the compounds and that the term is definite when read in view of the specification.[1] Importantly,

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[1] The terms were defined in the specification of the application at issue in *In Ex Parte Lewis et al.* as follows:

substituted alkyl groups . . . include hydroxyalkyl, haloalkyl, cyanoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, carboxyalkyl, carbalkoxyalkyl, alkoxyalkyl, aryloxyalkyl, alkylthioalkyl, arylthioalkyl, haloalkoxyalkyl, cycloalkylaminoalkyl, such as morpholinoalkyl, piperidinoalkyl, pyrrolidonylalkyl, and the

(continued...)

Applicants note that the definitions provided in *Ex Parte Lewis et al.* to define substituted alkyl groups and substituted aryl groups are analogous to the definitions used in the present application. Applicants respectfully submit that the term "substituted" does not render independent claim 1 or claims that depend therefrom indefinite. For the above reasons, Applicants respectfully request that the rejection of claims 1, 2, 4, 7-8, and 15-58 under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

Claims 4, 7-8, 11, 15, 23, 25, 27, 29, and 31-67 were rejected under 35 U.S.C. §112, first paragraph, for the reasons set forth on page 2 of the Office Action. The Examiner alleges that the specification, while being enabling for treating, breast, ovarian, and colon cancers, does not reasonably provide enablement for treating any and all cancers embraced by the claims. First, Applicants note that claims 43-50, 59, and 67 are not directed to methods of treating cancers. Rather these claims are directed to compounds (claim 59) or compositions comprising a compound and a pharmaceutically acceptable vehicle or diluent (claims 43-50 and 67). Accordingly, the rejection of these claims should be withdrawn. With regard to claims 4, 7-8, 11, 15, 23, 25, 27, 29, 31-42, 51-58, and 60-66 (the "method claims"), Applicants respectfully traverse the rejection.

Each of the method claims are limited to reciting cancers that are known to be treated by microtubule-stabilizing agents, which is recognized by the Examiner as treatable as in the case of Taxol® (*See, e.g.*, Amendment filed October 29, 2001, page 16 summarizing telephonic interview of October 24, 2001). Specifically, the method claims recite breast cancer, ovary cancer, colon cancer, head and neck cancer, lung cancer, melanoma, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, non-Hodgkin's lymphoma, multiple myeloma, prostrate cancer, bladder cancer, pancreatic cancer, and Karposi's sarcoma, all of which are known to be treated by Taxol® (*See, e.g.*, D.M. Bollag, Cancer Research, 55, No. 11, 2325-2333, 1995 (reference CC); G.H. Eltabbakh, Eur. J. Gynacol. Oncol., 20(1):18-9, 1999 ("Eltabbakh"); S. Glisson et al., Proc. Ann. Meet. Am. Soc. Clin. Oncol., 18:A814, 1999 ("Glisson"); G. Tortora et al., Cancer Res., 57,(22), 5107-11, 1997 ("Tortora"); E.K. Rowinski, Annu. Rev. Med., 48, 353-74, 1997 ("Rowinski"); K. Mross et al., Proc. Ann. Meet. Am. Soc. Clin.

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[1] (...continued)
like, carbamoxyalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, isothiazolonylalkyl, and the like.

By a substituted aryl group is meant an aryl group, such as benzene, naphthalene, or pyridine, having one or more of the hydrogen atoms on the aryl ring replaced by another substituent group. Examples of such substituent groups include halogen, nitro, lower alkyl, lower alkylacylamino, lower carbalkoxy, sulfamyl, and the like.

Oncol., 16:A776, 1997 ("Mross"); R. Panvichian et al., Proc. Ann. Meet. Am.Assoc. Cancer Res., 38:A1317, 1997 ("Panvichian"); R. Hajek, Cas. Lek. Cesk., 135(12), 393-6, 1996 ("Hajek"); D. Raghaven et al., Curr. Probl. Cancer, 19(1), 1-64, 1995 ("Raghaven"); L.A. Speicher et al., Cancer Res. 52(16), 4433-40, 1992 ("Speicher"); C.M. Spencer et al., Drugs, 48(5), 794-847, 1994 ("Spencer"); H.B. Newton, Expert Opin. Investig. Drugs, 9(12), 2815-29, 2000 ("Newton"); G.F. Fleming et al., J. Clin. Oncol., 19(4), 1021-9, 2001 ("Fleming"); http://health.yahoo.com/health/Drugs_Tree/Medication_or_Drug ("Yahoo"); and http://oncolink.upenn.edu/pdq_html/6/engl/600715.html ("Oncolink")). Copies of Eltabbakh, Glisson, Tortora, Rowinski, Mross, Panvichian, Hajek, Raghaven, Speicher, Spencer, Fleming, Yahoo, and Oncolink were enclosed with amendment filed on October 29, 2001. Clearly, these cancers are fully enabled by the specification since the epothilones of the invention are known to exert a microtubule-stabilizing effect similar to Taxol® and hence have cytotoxicity against rapidly proliferating cells such as tumor cells (*See, e.g.*, Specification, page 1, lines 11-21 and page 8, lines 20-22). Indeed, in the telephonic interview conducted on October 24, 2001 the Examiner agreed that the specification was enabling for cancers that are known to be treated by microtubule-stabilizing agents.

Although now moot given the interview and agreement with the Examiner, Applicants note that while the method claims were rejected on the basis that the specification does not provide an enabling disclosure for the general treatment of cancer, the rejection is in essence a rejection for lack of utility since a rejection under the "how to use prong" of 35 U.S.C. §112 incorporates, as a matter of law, the specification disclose a practical utility for the invention. *In re Ziegler*, 992 F.2d 1197, 1200-01 (Fed Cir. 1993) and MPEP 2107 IV. Compliance with 35 U.S.C. §101 and §112, first paragraph, is satisfied if an Applicant has asserted any specific and substantial utility that is credible. MPEP 2107.01. Furthermore, assertions of utility in a specification are presumed to be true and "must be taken as sufficient to satisfy the utility requirement of §101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." MPEP 2107.01 (citing *In re Langer*, 503 F.2d 1380, 1391). To overcome the presumption Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. MPEP 2101.01 III, A.

In the present case Applicants have asserted that the claimed epothilone molecules can be used to treat cancers that are known to be treated by Taxol®. Moreover, this utility is clearly credible. One of ordinary skill in the art would readily recognize that epothilone derivatives would

have this utility (*See, e.g.*, Bollag et al., *Cancer Research*, 55, 11 2325-33 ("Bollag"), reference CC on Form PTO 1449). Bollag discloses that epothilones A and B are mictrotubule-stabilizing agents having a neoplastic mechanism similar to that of paclitaxel (Taxol®). Clearly, one of ordinary skill in the art would find it credible that the claimed epothilone molecules would have a similar mechanism and could be utilized for the treatment of cancer and, in particular, for the treatment of the cancers specified in the method claims which are known to be treated by Taxol®. Thus, Applicants have complied with 35 U.S.C.§112, first paragraph, by asserting a specific and substantial utility that is credible. MPEP 2107.01. Moreover, the Examiner has failed to provide any factual basis or documentary evidence upon which it could be established that a person of ordinary skill in the art would not consider the asserted utility as being credible to overcome the presumption of utility.

Importantly, Applicants note that they have not claimed a *cure* for cancer, which might raise the level of scrutiny to that being applied by the Examiner. MPEP 2107, IV, 2. Rather, Applicants have claimed a method for the *treatment* of cancer. The MPEP clearly states that "[t]he fact that there is no known cure for a disease, however, cannot serve as the basis for a conclusion that such an invention lacks utility" and that "[a]n assertion that a claimed invention is useful in treating a symptom of an incurable disease may be considered credible by a person of ordinary skill in the art on the basis of a fairly modest amount of evidence or support." MPEP 2107, IV, 2. The important point is that "[o]nly those claims for which an asserted utility is not credible should be rejected." MPEP 2107, IV, 2. The method claims, directed to a method of treating specific cancers is credible. For the above reasons, Applicants submit that the method claims are fully enabled and respectfully request that the rejection under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

CONCLUSION

Applicants believe the application is in condition for allowance and earnestly requests reconsideration of the claims and allowance thereof. If the Examiner has any questions or suggestions to expedite allowance of this application, however, the Examiner is respectfully invited to call the undersigned to discuss the matter further.

No amendment fee is believed to be due for this submission. Should any fees be due, however, please charge the fees to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

Date: August 13, 2002

Paul E. Dietze (Reg. No. 45,627)
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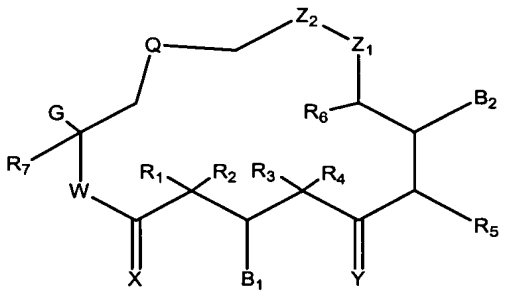
Appendix A

Pending claims for Application No. 09/084,542; filed May 26, 1998

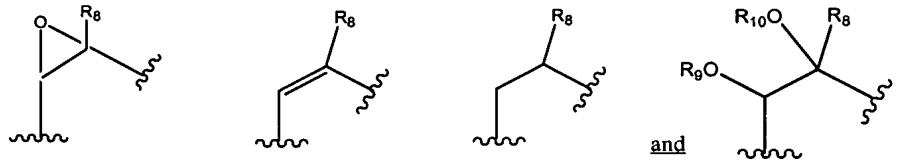
1. A compound of the formula:



V

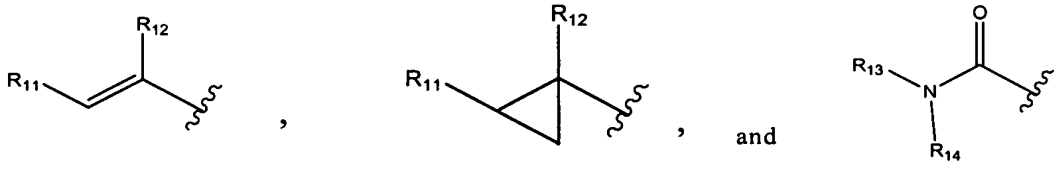
wherein:

Q is selected from the group consisting of:



and

G is selected from the group consisting of alkyl; substituted alkyl; substituted aryl; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;



W is O or NR_{15};

X is O or H, H;

Y is selected from the group consisting of O; H, OR_{16}; OR_{17}, OR_{17}; NOR_{18}; H, NOR_{19}; H, $NR_{20}R_{21}$; H, H; and CHR_{22}; wherein OR_{17}, OR_{17} can be a cyclic ketal;

Z_1 and Z_2 are independently CH_2;

B_1 and B_2 are independently selected from the group consisting of OR_{24}, $OCOR_{25}$, and

O-C(=O)-$NR_{26}R_{27}$, and when B_1 is OH and Y is OH, H, they can form a six-membered ring ketal or acetal;

R_1, R_2, R_3, R_4, R_5, R_7, R_{13}, R_{14}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{26} and R_{27} are selected from the group consisting of H, alkyl, substituted alkyl, and aryl, and when R_1 and R_2 are alkyl can be joined to form a cycloalkyl, and when R_3 and R_4 are alkyl can be joined to form a cycloalkyl;

R_6 is methyl;

R_9, R_{10}, R_{16}, R_{17}, R_{24}, R_{25} and R_{31} are selected from the group consisting of H, alkyl, and substituted alkyl;

R_{11}, R_{12}, R_{28}, R_{30}, R_{32}, and R_{33} are selected from the group consisting of H; alkyl; substituted alkyl; aryl; substituted aryl; cycloalkyl containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3-C_7 carbocyclic ring; and a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

R_8 is hydrogen or methyl;

R_{15}, R_{23} and R_{29} are selected from the group consisting of H; alkyl; substituted alkyl; aryl; substituted aryl; cycloalkyl containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3-C_7 carbocyclic ring; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur; $R_{32}C=O$; $R_{33}SO_2$; hydroxy; O-alkyl or O-substituted alkyl;

or pharmaceutically acceptable salts, hydrates, solvates or geometric, optical or steroisomers thereof;

with the proviso that compounds wherein

W and X are both O; and

R_1, R_2 and R_7 are H; and

R_3, R_4 and R_6 are methyl; and

R_8 is H or methyl; and

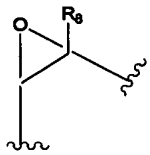
G is 1-methyl-2-(substituted-4-thiazolyl)ethenyl; and

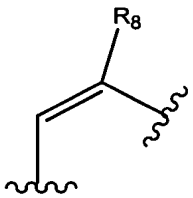
Q is as defined above

are excluded.

2. The compound of claim 1, wherein

Q is





X is 0;

Y is 0;

Z_1, and Z_2, are CH_2 and

W is NR_{15}.

3. A compound selected from the group consisting of:

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl)-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,10-dioxa-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl)-1,10-dioxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl)-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[l-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,11-dioxa-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-tetramethyl-16-[l-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,11-dioxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-3,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-3,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13,16-hexamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,16-pentamethyl-16-]l-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-6,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)etheny]]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-4,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-4,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[4.10]heptadecane-5,9-dione;

[4S-[4R*-7S*,8R,*9R-,15R*(E)]]-4,8-Dihydroxy-1,5,5,7,9,13-hexamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl-1-aza-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-1,5,5,7,9-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl)-13-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-13-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-(1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,BR*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-14-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-14-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazoly)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,(E)]]-4,8-Dihydroxy,5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*,7R*,10S*,11R*,12R*,16S*]]-N-Phenyl-7,11-dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecane-3-carboxamide;

[1S-[1R*,3R*,7R*,10S*,11R*,12R*,16S*]]-N-Phenyl-7,11-dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecane-3-carboxamide;

[4S-[4R*,7S*,8R*,9R*,15*]]-N-Phenyl-4,8-dihydroxy-5,5,7,9,13-pentamethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-16-carboxamide;

[4S-[4R*,7S*,8R*,9R*,15R*]]-N-Phenyl-4,8-dihydroxy-5,5,7,9-tetramethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-16-carboxamide;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazoly)cyclopropyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)cyclopropyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-hydxocymethy1-4-thiazolyl)ethenyl]-1-aza-13(Z)-cyclohexadecene-2,6-dione;
and the pharmaceutically acceptable salts, solvates and hydrates thereof.

4. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer,

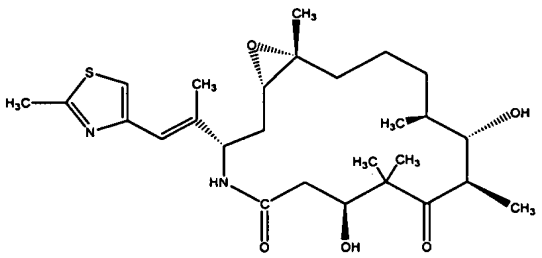
esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 1.

7. The method of claim 4, wherein the cancer is cancer of the breast, ovary, or colon.

8. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 2.

11. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 3.

14. A compound having the formula:



or a pharmaceutically acceptable salt, hydrate, solvate, geometrical isomer, optical isomer or stereoisomer thereof.

15. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said

treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 14.

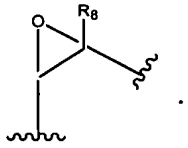
16. The method of claim 15, wherein the cancer is cancer of the breast, ovary, or colon.

17. The method of claim 8, wherein the cancer is cancer of the breast, ovary, or colon.

18. The method of claim 11, wherein the cancer is cancer of the breast, ovary, or colon.

19. The compound of claim 1, wherein G is 1-methyl-2-(substituted-4-thiazolyl) ethenyl group.

20. The compound of claim 1, wherein Q is



21. The compound of claim 1, wherein W is NR_{15}.

22. The compound of claim 1, wherein X and Y are each O.

23. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 19.

24. The method of claim 23, wherein the cancer is cancer of the breast, ovary, or colon.

25. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 20.

26. The method of claim 25, wherein the cancer is cancer of the breast, ovary, or colon.

27. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 21.

28. The method of claim 27, wherein the cancer is cancer of the breast, ovary, or colon.

29. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 22.

30. The method of claim 29, wherein the cancer is cancer of the breast, ovary, or colon.

31. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 1.

32. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 2.

33. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 3.

34. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 14.

35. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 19.

36. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 20.

37. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 21.

38. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 22.

39. The method of claim 4, further comprising administering one or more of a additional anti-cancer agent.

40. The method of claim 39, wherein the additional anti-cancer agent acts in a phase of the cell cycle other than the G_2-M phase.

41. The method of claim 40, wherein the additional anti-cancer is a thymidilate synthase inhibitor, a DNA cross linking agent, a topoisomerase I or II inhibitor, a DNA alkylating agent, a ribonuclase reductase inhibitor, a cytotoxic factor, or a growth factor inhibitor.

42. The method of claim 4, further comprising administering radiation therapy.

43. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable vehicle or diluent.

44. A pharmaceutical composition comprising the compound of claim 2 and a pharmaceutically acceptable vehicle or diluent.

45. A pharmaceutical composition comprising the compound of claim 3 and a pharmaceutically acceptable vehicle or diluent.

46. A pharmaceutical composition comprising the compound of claim 14 and a pharmaceutically acceptable vehicle or diluent.

47. A pharmaceutical composition comprising the compound of claim 19 and a pharmaceutically acceptable vehicle or diluent.

48. A pharmaceutical composition comprising the compound of claim 20 and a pharmaceutically acceptable vehicle or diluent.

49. A pharmaceutical composition comprising the compound of claim 21 and a pharmaceutically acceptable vehicle or diluent.

50. A pharmaceutical composition comprising the compound of claim 22 and a pharmaceutically acceptable vehicle or diluent.

51. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 1.

52. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 2.

53. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 3.

54. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 14.

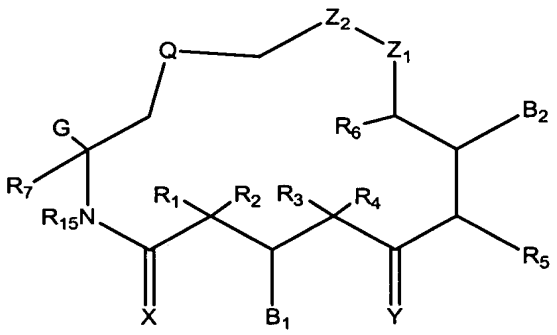
55. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 19.

56. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 20.

57. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 21.

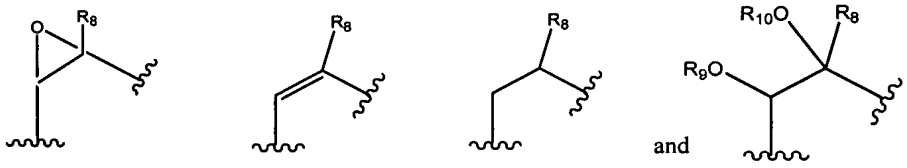
58. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 22.

59. A compound of the formula:

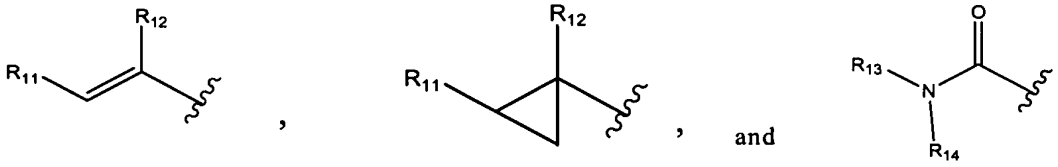


wherein:

Q is selected from the group consisting of:



G is selected from the group consisting of alkyl; substituted alkyl; substituted aryl; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;



X is O or H, H;

Y is selected from the group consisting of O; H, OR_{16}; OR_{17}, OR_{17}; NOR_{18}; H, NOR_{19}; H, $NR_{20}R_{21}$; H, H; and CHR_{22}; wherein OR_{17}, OR_{17} can be a cyclic ketal;

Z_1 and Z_2 are independently CH_2;

B_1 and B_2 are independently selected from the group consisting of OR_{24}, $OCOR_{25}$, and O-C(=O)-$NR_{26}R_{27}$, and when B_1 is OH and Y is OH, H, they can form a six-membered ring ketal or acetal;

R_1, R_2, R_3, R_4, R_5, R_7, R_{13}, R_{14}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{26} and R_{27} are selected from the group consisting of H, alkyl, substituted alkyl, and aryl, and when R_1 and R_2 are alkyl can be joined to form a cycloalkyl, and when R_3 and R_4 are alkyl can be joined to form a cycloalkyl;

R_6 is methyl;

R_9, R_{10}, R_{16}, R_{17}, R_{24}, R_{25} and R_{31} are selected from the group consisting of H, alkyl, and substituted alkyl;

R_{11}, R_{12}, R_{28}, R_{30}, R_{32}, and R_{33} are selected from the group consisting of H; alkyl; substituted alkyl; aryl; substituted aryl; cycloalkyl containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3-C_7 carbocyclic ring; and a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

R_8 is hydrogen or methyl;

R_{15}, R_{23} and R_{29} are selected from the group consisting of H; alkyl; substituted alkyl; aryl; substituted aryl; cycloalkyl containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3-C_7 carbocyclic ring; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur; $R_{32}C{=}O$; $R_{33}SO_2$; hydroxy; O-alkyl or O-substituted alkyl;

or pharmaceutically acceptable salts, hydrates, solvates or geometric, optical or steroisomers thereof.

60. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 59.

61. The method of claim 60, wherein the cancer is cancer of the breast, ovary, or colon.

62. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 59.

63. The method of claim 60, further comprising administering one or more of a additional anti-cancer agent.

64. The method of claim 63, wherein the additional anti-cancer agent acts in a phase of the cell cycle other than the G_2-M phase.

65. The method of claim 64, wherein the additional anti-cancer is a thymidilate synthase inhibitor, a DNA cross linking agent, a topoisomerase I or II inhibitor, a DNA alkylating agent, a ribonuclase reductase inhibitor, a cytotoxic factor, or a growth factor inhibitor.

66. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 59.

67. A pharmaceutical composition comprising the compound of claim 59 and a pharmaceutically acceptable vehicle or diluent.